REMARKS

Favorable reconsideration, reexamination, and allowance of the present patent application are respectfully requested in view of the foregoing amendments and the following remarks.

The above amendments are fully supported by the specification and therefore do not consitute new matter. More specifically, support can be found throughout the specification and original claims.

Options

The Examiner has re-opened prosecution following the filing by applicants of their appeal brief. Applicants have two options: (1) to file a reply under 37 CFR §1.111, or (2) to request reinstatement of the appeal. Applicants have chosen the first option, to file a reply under 37 CFR §1.111.

Rejection of claims 1-9 under 35 U.S.C. §112, 2nd paragraph

In paragraph 4a of the Official Action, claims 17 and 37-48 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for recitation of "an activity of making a bacterium having the protein L-threonine resistant", "an activity of a protein which makes the bacterium harboring the protein L-threonine resistant," or "an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant." The Examiner has stated that it is unclear as to the "activity" which imparts L-threonine or L-homoserine resistance to a protein.

Applicants have amended the claims for the purpose of clarifing the terms. Applicants also point the Examiner to page 6, line 5 through page 8, line 2, which explains very clearly the definition of L-threonine and/or L-homoserine resistance. Specifically, L-threonine resistance is defined by the instant application on page 7, lines 7-10 as a property whereby a bacterium is able to grow on a minimal medium containing L-threonine at a concentration at which a wild-type strain thereof would not grow, usually at >39mg/ml. L-homoserine resistance is defined by the instant application on page 7, lines 11-14 as a property whereby a bacterium is able to grow on a minimal

medium containing L-homoserine at a concentration at which a wild-type strain thereof would not grow, usually at >5mg/ml.

Applicants assert the claims are clear and defined, and therefore, respectfully request that this rejection be withdrawn.

In paragraph 4b of the Official Action, claims 38-39 and 44-45 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for recitation of "an activity of the protein". Applicants have amended the claims to clarify the antecedent basis of the "activity".

Applicants assert the claims are clear and defined, and therefore, respectfully request that this rejection be withdrawn.

In paragraph 4c of the Official Action, claims 39, 42, 45, and 48 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for recitation of "functions efficiently". From the plain meaning of the words, applicants assert it would be clear to a person of ordinary skill in the art that a promoter which causes the DNA to express the protein in an higher amount than another promoter in an efficient manner is a promoter which "functions efficiently". The claim recites a bacterium which is modified to increase an activity of a RhtC or Rhtb protein by substituting the promoters of these proteins' respective genes on the bacterial chromosome. Obviously, the new promoter functions efficiently if the expression of the protein is higher than that with the original promoter.

For these reasons, applicants assert the claims are clear and defined, and therefore, respectfully request that this rejection be withdrawn.

Rejection of claims 17 and 37-48 under 35 U.S.C. §112, 1st paragraph (written description)

In paragraph 5 of the Official Action, the Examiner rejected claims 17 and 37-48 under 35 U.S.C. §112, 1st paragraph for allegedly failing to comply with the written description requirement. The Examiner has alleged that the claims' recitation of any method for increasing DNA expression, and optionally wherein the modification is to

increase DNA copy number by any method or the modification is to substitute the promoter sequence of the gene coding for the protein with any nucleic acid that promotes DNA expression is insufficiently described. The Examiner alleges that the claims are drawn to a genus for which an insufficient number of representative species is disclosed. The Examiner provides examples of (1) all nucleic acids which hybridize under recited conditions to nucleotides 187-804 of SEQ ID NO: 3, (2) the genus of E.coli bacterium having modifications to increase DNA expression, increased copy number, or promoter substitution, and (3) the bacterial host cell which comprises an expression vector, wherein the expression vector has a nucleic acid encoding the polypeptide of SEQ ID NO: 2 or 4.

Applicants respectfully disagree with the Examiner's allegations and provide the following response. With regard to the use of any means to increase DNA expression, the specification exemplifies two means for increasing DNA expression: amplification of the copy number of rhtC gene and substitution of a promoter sequence which functions efficiently on a chromosome with a promoter sequence which functions efficiently (see page 14, line 15 to page 15, line 8). Furthermore, the specification exemplifies a means for amplification of the copy number of the rhtC gene: introduction of a multi-copy vector, a phage, or a transposon comprising the rhtC gene into a bacterium (see page 15, line 21 to page 16, line 18).

Applicants assert that the crux of the present invention is the discovery that the rhtB and rhtC gene, when expressed at a higher level than wild-type in E. coli, act to increase production of L-amino acids, particularly L-threonine and L-homoserine. The crux of the invention is not how to increase expression of a particular DNA species in E. coli. This is not the crux of the invention, most notably, because this is a known procedure that has been practiced in the art for many, many years. "A patent need not teach, and preferably omits, what is well known in the art." *Spectra Physics, Inc. v. Coherent, Inc.* 827 F.2d 1524 (Fed. Cir. 1987). Skilled art workers know how to increase the expression of a target DNA, and such methods include increasing the copy number by using a multi-copy vector, or using a different promoter. Many highly efficient promoters, particularly in E. coli, are well-known in the art. It is not necessary to teach or describe what is well-known in the art. It is unnecessary for applicants to describe to any extent more than what is currently described in the specification the methods for

increasing expression of the target DNA. Two methods are exemplified, both well-known in the art, and this is sufficient to support a genus for a method (increasing DNA expression) which is well-known in the art. The skilled art worker can go to the prior art to determine other possible methods for increasing DNA expression, other promoter sequences which would increase efficiency of expression, or other methods for increasing copy number. It is not necessary for applicants to provide a laundry list of the well-known methods.

With regard to the use of any promoter sequence, applicants have attached two exhibit references: Cunning et al. (J. Bacteriol. 180:4564-70 (1998)) and W:alker et al. (J. Bacteriol. 174:1119-23 (1992)). These references specifically disclose methods for use of alternative promoters, and substituting a promoter sequence for a wild-type promoter. As shown in these references, one skilled in the art can select a desirable promoter sequence and substitute a promoter sequence, as such decisions and practice methods were clearly within the skill of the skilled art worker. Specifically, such methods were being practiced in E. coli in 1992, as evidenced by the Walker et al reference. Clearly, the skilled art worker could make such routine decisions in 1999 when the instant application was filed.

For these reasons, applicants assert the claims are clear and defined, and therefore, respectfully request that this rejection be withdrawn.

Rejection of claims 17 and 37-48 under 35 U.S.C. §112, 1st paragraph (enablement)

In paragraph 7 of the Official Action, the Examiner rejected claims 17 and 37-48 under 35 U.S.C. §112, 1st paragraph for allegedly failing to comply with the enablement requirement. The Examiner alleges that the specification does not reasonably provide enablement for all DNAs as recited in the claims and all modified bacteria as encompassed by claims 37-48.

As explained above, applicants assert that the techniques for increasing DNA expression, such as the use of known promoters in E.coli. for achieving efficient expression of a target sequence, are well-known in the art, and therefore, the disclosure, in combination with the knowledge in the art, provides sufficient enablement for practicing the instant invention. One of ordinary skill in the art has sufficient

information from the prior art and his or her own high level of skill and knowledge, and further combined with applicant's specification to practice the claimed invention. Methods of increasing expression of DNA are well-known in the art.

With regard to the enablement of DNA species which hybridize to SEQ ID NO: 3 under the recited hybridization conditions, it is unclear what the bases are for such a rejection. On page 10 of the office action, the Examiner alludes to such a rejection in the "high level of unpredictability in the art" section, where the Examiner discusses predictability of making changes in a protein's amino acid sequence to obtain the desired activity. The Examiner has not specifically recited that the claimed hybridization conditions give rise to this rationale, but applicants will assume such a rejection.

Specifically, attached please find a FASTA sequence search of SEQ ID NO. 3, which demonstrates the highly conserved nature of the SEQ ID NO.3 sequence among gram-positive bacteria. Therefore, there is much information due to this conservation which can be surmised by the skilled art worker to determine the locations amenable to mutation or change. For example, regions which are highly conserved are most likely necessary for the function and activity of the protein, and therefore, only very conservative changes, or none at all, should be made. Regions where variation occur are most likely not necessary for function, and therefore, conservative changes, as well as non-conservative changes, can most likely be made. Such analysis is well within the skill level of the skilled art worker in this field, and therefore, one of ordinary skill in the art would be able to determine regions of the encoded protein and determine which regions are amenable to changes without negatively effecting the activity of the protein.

For these reasons, applicants assert the claims are enabled by the specification, and therefore, respectfully request that this rejection be withdrawn.

REMARKS

Favorable consideration, examination, and allowance of the present patent application are respectfully requested. Applicants respectfully submit that the present patent application is in condition for allowance. An early indication of the allowability of the present patent application is therefore respectfully solicited.

If the patent examiner believes that a telephone conference with the undersigned would expedite passage of the present patent application to issue, they are invited to call on the number below.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the undersigned authorizes the necessary charges to our deposit account 50-3077.

Respectfully submitted,

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